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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
08/991,143	12/16/97	CONTI-FINE	B	600.423US1

HM12/0218

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EXAMINER	
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ART UNIT	PAPER NUMBER
1644	10

DATE MAILED: 02/18/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/991143	CONTI-FINE ET AL.
Examiner: RABIN	Group Art Unit: 1644

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Peri d f r Response

A SHORTENED STATUTORY PERIOD FOR RESPONSE IS SET TO EXPIRE -3- MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a response be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for response is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to respond within the set or extended period for response will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 11/23/98.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disp sition of Claims

☒ Claim(s) 1-33 is/are pending in the application.

Of the above claim(s) 19-30 and 32-33 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-18 and 31 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 3 and 9

☒ Notice of References Cited, PTO-892

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other _____

Office Action Summary

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of Group I (Claims 1-16 and 31 in Paper No. 8 is acknowledged. The traversal is on the ground(s) that all the claims encompass a unitary inventive concept and that a search of all the claims would not impose a serious burden on the examiner. This is not found persuasive for the same reasons as set forth in the restriction requirement (Paper No. 6) and because the methods involve different steps and different ingredients. Further, the different methods require different fields of search. The required searches cover divergent subject matter; searches of one invention do not overlap entirely searches of other areas. However, upon reconsideration, Claims 17 and 18 appear to be drawn to the same subject matter as Claims 1-16; therefore, Group II, Claims 17 and 18, is rejoined to Group I.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-33 are pending. Claims 19-30 and 32-33 are withdrawn, as drawn to a non-elected invention. Claims 1-18 and 31 are currently under examination.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 3 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 3 and 8 recite the limitation "said antibody" twice in Line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-3, 6, 8, 9, 13, 14, 17, and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Norman *et al.* [Am. J. Respir. Crit. Care Med. 154: 1623-1628 (Dec 1996)].

Norman *et al.* teach a method to tolerize a mammal to an antigen associated with undesirable antibody production which is specific for a particular antigen, Fel d 1, the principal allergen of cat dander, in order to inhibit an indication associated with undesirable antibody production, *i.e.*, allergy. Norman *et al.* teach that their treatment protocol is the first demonstration that peptides designed to induce T cell tolerance can alter the manifestations of a human immunologic disease and that the use of molecular

species directed specifically toward T cell receptors is novel (Page 1628, Last paragraph, in particular). Norman *et al.* teach administering to a human afflicted with allergy to cats a dosage form comprising an amount of at least one epitope peptide effective to inhibit at least one symptom of cat allergy. Norman *et al.* teach the administration of two peptides which contain the dominant T-cell epitopes. The peptides comprise less than the sequence of the antigen (Page 1623, Abstract and Column 2, and Figure 1, in particular). Changes in the Nasal Symptom Score and Lung Symptom Score of individual patients were measured. Patients treated with peptides had less severe symptoms (Page 1625, Column 2, in particular). Norman *et al.* teach that administration of the peptides does not increase synthesis of pathogenic antibody to the native Fel d 1 antigen (Page 1626, Lines 3-4, in particular).

The reference teaching anticipates the claimed invention.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not

commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1, 2, 7, 10, and 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Norman *et al.* [Am. J. Respir. Crit. Care Med. 154: 1623-1628 (Dec 1996)] in view of Metzler *et al.* [International Immunol. 5 (9): 1159-1165 (Mar 1993)], Ma *et al.* [J. Neuroimmunol. 58: 51-60 (1995)], and Hetzel *et al.* [Int. Arch. Allergy Immunol. 107: 275-277 (May-June 1995)].

Norman *et al.* have been discussed, *supra.*

Norman *et al.* do not teach nasal administration of peptides nor the suppression of an allergic response to a fungal antigen. However, Metzler *et al.* teach a method of inhibiting experimental autoimmune encephalomyelitis (EAE) by administering peptides via mucosal surfaces, *i.e.*, nasal administration. Metzler *et al.* teach that peptide inhalation of the peptide Ac1-9 or Ac1-11 inhibits not only EAE induced by subcutaneous injection of the encephalitogenic peptide but also disease induced by a complex mixture of potential auto-antigens such as spinal cord homogenate. Metzler *et al.* teach that the same epitope that is capable of inducing EAE in a priming protocol can function as a powerful tolerogen upon inhalation (Page 1162, Figure 3 and Page 1163, Column 2, in particular). Hetzel *et al.* teach that delivery of antigens via the mucosae of the alimentary or respiratory tracts induces tolerance to systemic challenge. Hetzel *et al.* teach that nasal therapy would be practical and enable self-administration by allergic patients. Hetzel *et al.* teach that "in a murine system of *in vivo* tolerance to the allergen *Der p* I, oral or nasal exposure to dominant epitopes rendered both naive and primed mice unresponsive to s.c. challenge with *Der p* I in adjuvant and the tolerance appeared to 'spread' to subdominant epitopes" (Page 276,

Column 2, in particular). Ma *et al.* teach that "[I]nduction of tolerance is a highly attractive therapy because of its natural and powerful immunosuppression. Compared with oral tolerance, nasal tolerance against EAMG has advantages in the sense that it requires much smaller doses of AChR, is more convenient to induce and doses not require STI which is used to inhibit the degradation of AChR in the gastrointestinal tract ... This approach should also be feasible in MG [human myasthenia gravis], and the nasal administration of the autoantigen could be advantageous" (Page 59, Last paragraph, in particular). Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to be motivated to substitute Metzler's method of nasally administering antigen for the method of administering antigen utilized by Norman *et al.* in order to inhibit the allergic response in the most practical and successful way. A person of ordinary skill in the art would have had a reasonable expectation of success of being able to inhibit the allergic response by nasally administering peptides because of the success of Norman *et al.* in inhibiting an allergic response in response to administering peptides, because of the success of both Metzler *et al.* Ma *et al.* in utilizing nasal administration of whole antigen and peptide epitopes to suppress an autoimmune response, and the teachings of Hetzel *et al.* indicating the advantages of nasal administration for allergy patients. Further, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to be motivated to substitute fungal antigen peptides for the peptides of the allergen Fel d 1, the allergen *Der p* I, and the autoantigen AChR, taught by Norman *et al.*, Hetzel *et al.*, and Ma *et al.*, respectively, because one of ordinary skill in the art would have had no reason to expect that fungal peptides would behave differently. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

9. Claims 1-5, 8, 11-15, 17, 18, and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ma *et al.* [J. Neuroimmunol. 58: 51-60 (1995)] in view of Moiola *et al.* [J. Immunol. 152 (9): 4686-4698 (May 1994)] and Bellone *et al.* [Eur. J. Immunol. 21: 2303-2310 (1991)].

Ma *et al.* teach a method to tolerize a mammal to an antigen associated with pathogenic antibody production specific for the endogenous antigen, acetylcholine receptor (AChR) in order to inhibit a disease associated with pathogenic antibody production, *i.e.*, experimental autoimmune myasthenia gravis (EAMG), comprising: administering to a mouse afflicted with EAMG, a dosage form of AChR effective to suppress at least one symptom of the disease and the activity of T cells specific for the antigen (Page 54, Figures 1-2, and Page 55, in particular). Ma *et al.* teach that such administration is effective to reduce or inhibit the amount of pathogenic antibody produced (Page 55, Figure 3; Page 56, Tables 1-2; and Page 58, Column 2, Lines 40-48, in particular). Ma *et al.* teach that the dosage form is administered to the respiratory tract. Ma *et al.* teach that "[I]nduction of tolerance is a highly attractive therapy because of its natural and powerful immunosuppression. Compared with oral tolerance, nasal tolerance against EAMG has advantages in the sense that it requires much smaller doses of AChR, is more convenient to induce and doses not require STI which is used to inhibit the degradation of AChR in the gastrointestinal tract ... This approach should also be feasible in MG [human myasthenia gravis], and the nasal administration of the autoantigen could be advantageous" (Page 59, Last paragraph, in particular). Ma *et al.* teach that administration of the peptides does not increase synthesis of pathogenic antibody to the AChR antigen (Page 55, Figure 3; Page 56, Tables 1-2; and Page 58, Column 2, Lines 40-48, in particular).

Ma *et al.* do not teach administering at least one epitope peptide wherein the sequence of the epitope peptide comprises an immunodominant epitope sequence and where the

peptide comprises less than the sequence of the antigen. However, Moiola *et al.* teach that because "T cells recognize denatured sequence segments of protein Ags, and the human muscle AChR sequence is known, MG [myasthenia gravis] is an ideal system to study the $CD4^+$ epitope repertoire in a human autoimmune response (Page 4686, Column 2, in particular). Moiola *et al.* teach the individual residues within four immunodominant AChR regions (α48-67, α304-322, γ75-94, and γ321-340) involved in formation of epitopes in different patients, of the same or of different DR haplotype (Page 4687, Column 1, in particular). Bellone *et al.* teach that Mα304-322 is "highly conserved in human, murine, and Torpedo AChR, and one immunodominant Th epitope in human MG is within the sequence segment α304-322 (Page 2309, Lines 10-14, in particular). Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to be motivated to substitute the peptides of Moiola *et al.* and Bellone *et al.* for the Torpedo AChR of Ma *et al.* A person of ordinary skill in the art would have had a reasonable expectation of success of being able to tolerize a human to AChR peptides in order to inhibit myasthenia gravis because of the success of Ma *et al.* in inhibiting EAMG and because of the teachings of both Moiola *et al.* and Bellone *et al.* pertaining to immunodominant peptide epitopes. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

10. No claims are allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Evelyn Rabin, Ph.D. whose telephone number is (703) 305-6811. The examiner can normally be reached on Monday through Thursday from 7:30 AM to 6:00 PM.

12. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached on (703) 308-3973. The FAX number for this Technology Center is (703) 305-3014 or (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology Center receptionist whose telephone number is (703) 308-0196.

Evelyn Rabin, Ph.D.
Patent Examiner
February 16, 1999

EVELYN RABIN
PATENT EXAMINER